100 to 200 gm PEG per two liters.) The article ends, "...the use of polyethylene glycol 4000 prophylactically after any moderately abundant digestive hemorrhage may be proposed in order to avoid the incidence of hepatic encephalopathy.".

Applicant's rejected claims specify that the claimed methods comprise orally administering the PEG compositions to an HE patient. In contrast, Roblin's disclosed method is limited to the use of a gastric lavage administered through a gastric probe (tube) to evacuate intestinal blood resulting from acute and abundant digestive hemorrhage and thereby reduce the elevated ammonia levels and HE events associated with such episodes. Not only does Roblin not suggest that oral administration is an alternative (it appears his patient was in a coma), he states, "The only requirement [for administration] is the placement of a gastric probe..." (line 27). In fact, the Roblin treatment is applied only following hemorrhaging, which is typically accompanied by coma or incipient coma, when liquids cannot be orally administered. Roblin specifies his goal as the treatment of HE during digestive hemorrhaging, wherein increased ammonemia is a main etiological factor and early treatment is essential(paragraph 2 of Roblin's Letter to the Editor).

To clarify that Applicant's claimed method for treatment does not include administration by gastric probe or other feeding tube as in Roblin, claim 1 now specifies that the composition orally administered is a "liquid drink"composition. Antecedent basis for the added language is found on page7, lines 4-6. It is accordingly respectfully submitted that Roblin does not teach Applicant's claimed invention within the meaning of 35 USC §102(a), and reconsideration and withdrawal of this rejection is therefore requested.

The Examiner has further rejected Claims 1, 4, 19, 22 and 23 (method claims 1 and 4 and claims dependent thereupon), under 35 USC 103(a) as being unpatentable over Roblin, *et al.* (*op.cit.*) in view of Vicidomini *et al.*, EP 1230918, on the grounds that Roblin teaches the use of PEG to treat HE and the '918 patent teaches the use of an aqueous solution containing lactulose to treat HE, especially porto-systemic HE.

Applicant agrees that the '918 patent teaches the use of lactulose for treatment of HE; this has long been the standard treatment as discussed at length in Applicant' specification. Both Applicant and the EP patent [0006] teach the oral administration of lactulose before an HE patient's condition deteriorates enough to compromise the swallowing mechanism, typically on a continuing basis of regular oral doses. However, as noted above, Roblin teaches the use of a PEG colon lavage solution introduced by gastric tube into a comatose patient following hemorrhaging, to evacuate intestinal blood and thereby lower the high blood ammonia levels associated with hemorrhage-related HE. Clearly, as a practical matter, chronic ammonemia cannot be treated or alleviated by Roblin's methods.

A finding of *prima facie* obviousness requires at least some teaching which would prompt one skilled in the art to combine these two treatment methods. There is, however, no teaching in either of the cited references which would suggest using Roblin's PEG lavage for evacuating intestinal blood with a lactulose composition formulated for oral administration for the purpose of controlling or preventing chronic ammonemia. In fact, these two methods cannot be combined and there would thus be no motivation to combine the Roblin and Vicidomini materials. Roblin speaks only of colon lavage solutions, which are used in high-strength, high-volume amounts on a one-time basis, primarily as cleansers prior to procedures involving the intestinal tract, usually the bowel. Further, his treatment, as noted above, is exclusively applied to emergency cases involving "abundant digestive hemorrhage" and requires a gastric tube for administration; again, lower ammonia levels are observed, but result from the flushing of intestinal blood (Roblin, paragraph 2: "That [increased ammonemia] is why, in the presence of acute digestive hemorrhage, evacuation of intestinal blood is often used."). Accordingly, reconsideration and withdrawal of this ground of rejection is respectively requested.

Assuming *arguendo* that the Examiner has presented a case of *prima facie* obviousness, Applicant notes that the methods of the present invention provide treatments for HE which

significantly reduce the side effects of orally administered lactulose solutions as used in the prior art and which simultaneously enable the achievement and maintenance of clinically-acceptable plasma ammonia levels in patients with hepatic or other insufficiency, results which could not be expected from the prior art disclosures. As stated in the specification, page 7, the methods of the invention can reduce toxic plasma ammonia levels by about 25% to 50% or more to clinically-acceptable stable levels, while at the same time alleviating the constipation which is a common affliction with HE patients.

The Examiner is also referred to the Example, which details the treatment of a cirrhosis patient with HE. Of particular interest is the observation that the patient's very poor condition when presenting was in good part due to poor compliance: "the patient has a difficult time taking lactulose [as conventionally administered] because of the nausea, abdominal discomfort, and bloating ...and its unpleasant taste." After treatment according to the invention, her blood ammonia levels, which had been high, were under control at satisfactory clinical and therapeutic levels, with no clinical signs of HE. This is at least in part attributed to high patient compliance owing to the absence of bloating and nausea and crampy sensations associated with her previous lactulose intake, and the acceptable taste of the lactulose composition.

Applicant's specification discusses the use and drawbacks of lactulose to treat HE as extensively reported in the prior art, including its poor taste. EP '918 elaborates on such lactulose side effects incurred with daily doses of this saccharide in the prodromic stage: "...although [lactulose and lactitol] do not have the toxicity of neomycin, they are nevertheless also associated with unpleasant phenomena such as, for example, nausea, vomiting, flatulence, diarrhoea and abdominal pains." [0012]. In an effort to retain the highly desirable properties of lactulose in HE treatment, including both its osmotic properties and its ability to convert free ammonia in the intestinal tract to non-toxic substances, while at the

same time reducing its side effects, Applicant, a gastroenterologist, thought to combine PEG, also an osmotic, with a reduced dosage of lactulose. The combination provided a composition which retains the ability to draw free ammonia from the bloodstream into the gut by osmosis and to neutralize this free ammonia with lactulose breakdown acids while also accelerating the evacuation of the gut. These properties provide compositions which are excellent in their ability to mount a two-pronged counterattack against a dietary overload of proteins by hastening their movement through the intestinal tract while at the same time neutralizing ambient free ammonia generated by their digestion. Most advantageously, the compositions have a significantly decreased incidence of adverse side effects.

None of these results were foreseen or hinted at in the prior art applied and it is submitted that these results are unexpected and sufficient to rebut any presumption of obviousness. Accordingly, reconsideration and withdrawal of the rejection of claims 1, 4, 19, 22 and 23 (method claims 1 and 4 and claims dependent thereupon), under 35 USC 103(a) as being unpatentable over Roblin, *et al.* (*op.cit.*) in view of Vicidomini *et al.*, EP 1230918, is respectfully requested.

The Examiner further rejects claims 1-25 under 35 USC 103(a) as being unpatentable over Roblin, *et al.* (*op.cit.*) in view of Vicidomini *et al.*, EP 1230918, on the 35 USC 103(a) grounds *supra*, and further in view of Pelham *et al.* , US 2005/0152989 on the additional grounds that Pelham *et al.* teaches a composition of laxative and fiber for the treatment of irritable bowel syndrome, which includes constipation, containing lactulose and polyethylene glycol, referring to the Abstract, paragraph [0004] and [0013]. The Examiner states, "The reference teaches that lactulose is a poorly absorbable <u>disaccharide (i.e. fiber)</u> (paragraph [0022]), and that PEG is an osmotic laxative...". [Emphasis added.]

This rejection is based on an erroneous reading of Pelham *et al.* Lactulose is a double sugar (disaccharide), not a fiber. Note the Examiner's discussion of Vicidomini in this rejection, where it is stated that lactulose is added to spring

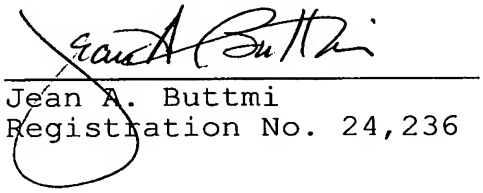
water "in crystalline form"; also note the definition of fiber in ¶ [0027] of Pelham: "polysaccharides and lignins". ¶ [0022] contains lactulose in a list of "useful osmotic laxatives"; PEG is recited as an osmotic laxative in ¶[0023]. The compositions of Pelham comprise an osmotic laxative and a fiber; Pelham does not teach PEG and lactulose compositions.

Reconsideration and withdrawal of this rejection is accordingly requested.

Claims 1-9 have been amended for clarity and consistency. Claim 10 has been broadened. Antecedent basis for new claims 26-28 is found on page 7, lines 16-26 of the specification. New claims 29 and 30 are claims to the matter deleted from amended claim 1.

It is respectfully submitted that the claims as presented herein are in condition for allowance and early favorable action is earnestly solicited.

Respectfully submitted,



Jean A. Buttmi
Registration No. 24,236

November 1, 2005

HOFFMAN, WASSON & GITLER, PC
2461 South Clark Street
Suite 522 - Crystal Center 2
Arlington, VA 22202
(703) 415-0100

Attorney's Docket: A-8636.Amendment/cat